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REVIEW ARTICLE

Review of the clinical significance of respiratory virus infections in newborn infants

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ABSTRACT

Respiratory viruses have been recognised as causative agents for a wide spectrum of clinical manifestations and severe respiratory compromise in neonates during birth hospitalisation. Early-life respiratory virus infections have also been shown to be associated with adverse long-term consequences.

Conclusion: Preventing virus infections by intensifying hygiene measures and cohorting infected infants should be a major goal for neonatal intensive care units, as well as more common use of virus diagnostics. Active virus surveillance and long-term follow-up are needed to ascertain the causality and exact underlying mechanisms for adverse long-term consequences.

INTRODUCTION

Newborn infants, particularly those born prematurely, are susceptible to bacterial and viral infections due to their immature and inexperienced innate and adaptive immune systems. Preterm infants also have an inadequate protection against infection agents through maternal immunity. They are also subjected to repeated invasive procedures that interfere with the body's protective mucosal and epithelial barriers. These all augment the risk of infections. Moreover, the innate cytokine response against viruses in a neonate can be inadequate or, conversely, overwhelming and is associated with increased disease severity (1).

The source of respiratory virus infection is often unknown, but viruses are likely to be transmitted either vertically *in utero* from the infected mother or horizontally after birth from the family members, staff members or other patients. Although the clinical course of a respiratory virus infection in a neonate is usually mild, viruses can also cause significant morbidity and potentially fatal illnesses in otherwise healthy infants. Further, early-life viral respiratory infections have been shown to be associated in susceptible individuals with lung function abnormalities, particularly recurrent wheeze and asthma, at follow-up (2). During the past decade, our understanding of other long-term sequelae of respiratory virus infections during infancy has also increased.

Abbreviations
NICU, Neonatal intensive care unit; PCR, Polymerase chain reaction; RSV, Respiratory syncytial virus.

The contribution of respiratory viruses to clinical signs of infection among infants in neonatal intensive care units (NICUs) has been poorly recognised (3). However, outbreaks of common respiratory viruses among hospitalised infants have been widely described, although surveillance for respiratory viruses has been mainly performed only among infants with respiratory symptoms. Nosocomial respiratory virus infections are associated with higher risk of morbidity and also with a longer length of stay in hospital (4). In this review, we summarise the current knowledge of early-life respiratory virus infections in neonates.

OCCURRENCE AND AETIOLOGY OF EARLY-LIFE RESPIRATORY VIRUS INFECTIONS AMONG HOSPITALISED INFANTS

A review published by Civardi et al. (5) in 2013 reported 32 respiratory virus outbreaks in NICUs detected with a variety of diagnostic methods. The respiratory syncytial

Key notes

- Respiratory virus infections are more common during neonatal hospitalisation than earlier recognised and infections can be associated with negative outcomes and long-term consequences on the child.
- There is an urgent need for more common use of virus diagnostics.
- All available preventive and curative modalities against viral respiratory tract infections during the neonatal period should be immediately implemented.

virus (RSV), enteroviruses and adenovirus were the most common causative agents. Significant nosocomial outbreaks of rhinovirus have also been described in NICUs (6). Fortunately, nosocomial influenza outbreaks have only been reported on rare occasions (7). According to individual case reports, outbreaks of all major respiratory viruses among hospitalised infants have been described (5). At its worst, an epidemic may result in the temporary closure of a NICU. In one adenovirus-induced epidemic, a NICU was closed for four weeks (8).

Seven studies have reported the occurrence of respiratory virus infections among infants, mostly while they were hospitalised at birth and detected with multiplexed polymerase chain reaction (PCR) tests (4,6,9–13). These studies are summarised in Table 1 and show that 60% of the infants were treated in NICUs and 40% in other neonatal units. A total of 788 premature and term infants were studied for respiratory viruses in their nasopharynx: three of these seven studies included all infants with signs of respiratory tract infection, two studies included all infants with suspected nosocomial sepsis and two studies included all infants in the NICU. In 16% (range 10–52%) of the cases, a respiratory virus was detected and this was mostly diagnosed in symptomatic infants. In two studies, respiratory viruses were also detected in asymptomatic premature infants in whom the infection was unsuspected and not clinically recognised (4,10). All common respiratory viruses were found in NICUs, but rhinovirus (36%), parainfluenza viruses (28%) and RSV (20%) accounted for more than 80% of the detected viruses. It is important to stress that in one study the detection of a respiratory virus during birth hospitalisation correlated with a higher incidence of bronchopulmonary dysplasia (4). Furthermore, in some studies there was evidence for nosocomial transmission despite strict infection control practices (4,9).

ACUTE MANIFESTATIONS OF RESPIRATORY VIRUS INFECTIONS

Most respiratory virus infections in neonates are confined to the upper respiratory tract and the first clinical symptoms are usually rhinorrhea, congestion and a cough (14). An upper respiratory tract infection may be accompanied by fever, which causes lethargy and poor feeding. About one-third of infants develop lower respiratory tract symptoms such as wheeze, breathlessness and respiratory distress (9–14). In the most severe cases, mechanical ventilation and even extracorporeal membrane oxygenation are needed because of respiratory compromise. In neonates, a respiratory virus infection can also present as a systemic illness that resembles bacterial sepsis (11,13). The most common systemic signs include apnoea, tachypnoea, temperature instability, lethargy and poor feeding. In addition to these nonspecific symptoms, the first signs in hospitalised infants can be an increased need of ventilator support or hypoxaemia. Extrapulmonary manifestations of respiratory virus infections may also occur. The most common of these are meningoencephalitis, perimyocarditis, hepatitis, coagulopathy, myositis, skin symptoms and gastroenteritis (14). These manifestations are due to the viraemic spread of certain respiratory viruses, such as enteroviruses, the adenovirus, bocavirus-1 and parechovirus. The common respiratory viruses and their clinical pictures in neonates are presented in more detail in Table 2 (15–24).

The severity of a respiratory virus infection is modified by both genetic and environmental risk factors. Well-known risk factors for severe illness include prematurity, young age

Table 1 Occurrence of respiratory virus infections diagnosed with multiplex polymerase chain reaction method in neonatal intensive care units

Study	Symptoms	Infants studied Duration of the study	Viruspositive/examined	Viruses
van Piggelen et al. (6) 2010, Netherlands	Signs of respiratory tract infection	All infants Five years	22/62 (41%)	Rhinovirus (n = 11), RSV (n = 8), others (n = 3)
Steiner et al. (9) 2012, Austria	Signs of respiratory tract infection	Preterm infants 11 months	16/106 (15%)	Rhinovirus (n = 15), metapneumovirus (n = 1)
Bennett et al. (4) 2012, USA	All infants in the NICU twice a week	<33 gestational age preterm infants One year	26/50 (52%) 30% asymptomatic	Parainfluenza viruses (n = 20), RSV (n = 15), metapneumovirus (n = 9), others (n = 11)
Smit et al. (10) 2013, Netherlands	All infants in the NICU at admission	All infants One year	34/334 (10%)	Parainfluenza viruses (n = 15), rhinovirus (n = 7), RSV (n = 6), others (n = 6)
Kidszun et al. (11) 2014, Germany	All infants with suspected nosocomial sepsis	All infants One year six months	6/60 (10%)	Picornavirus (n = 5), RSV (n = 1)
Kujari et al. (12) 2014, Finland	Signs of respiratory tract infection	All infants Two years six months	14/76 (18%)	Rhinovirus (n = 7), parainfluenza viruses (n = 6), RSV (n = 2), coronavirus (n = 1)
Ronchi et al. (13) 2014, USA	All infants with suspected nosocomial sepsis	All infants One year	8/100 (8%)	Entero-/rhinoviruses (n = 2), rhinovirus (n = 2) coronavirus (n = 2), parainfluenza viruses (n = 2)

NICU = Neonatal intensive care unit; RSV = Respiratory syncytial virus.

Table 2 The respiratory viruses detected in infants during acute respiratory infections

Virus	Seasonality	Risk factors for severe disease
Adenovirus	Throughout the year	Young age (*in utero* transmitted disease)
Bocavirus-1	Moderate winter seasonality	Pre-existing medical condition, nosocomial disease
Coronavirus	Marked winter seasonality	Prematurity
Enteroviruses	Marked late summer and early fall seasonality	Young age (*in utero* transmitted disease)
Metapneumovirus	Marked winter seasonality	Prematurity, young age, pre-existing severe medical condition, nosocomial disease
Parechovirus	Moderate winter seasonality	Prematurity
Influenza A, B	In temperate zones, annual epidemics during winter months	Prematurity, CLD
Parainfluenza 1–4	Moderate spring seasonality	Prematurity
Respiratory syncytial virus	Annual winter outbreaks	Prematurity, CLD, CHD*, CF, congenital immune defects, neuromuscular disorders
Rhinovirus	Through the year, especially during early fall and spring	Prematurity, diseases affecting lung function
Virus	**The most common clinical signs in neonates**	**Acute complications**
Adenovirus	Nonspecific febrile illness – sepsis-like disease, rhinorrhea, congestion, cough, temperature instability, poor feeding, neurologic signs (irritability, lethargy)	Pneumonia, disseminated disease
Bocavirus-1	Rhinorrhea, congestion, cough, bronchiolitis, fever	Pneumonia, AOM, meningoencephalitis
Coronavirus	Rhinorrhea, congestion, cough, bronchiolitis, fever, apnoeas	Pneumonia, CNS manifestations (febrile convulsions, meningoencephalitis), laryngitis
Enteroviruses	Nonspecific febrile illness – sepsis-like disease, respiratory symptoms (pharyngitis, bronchiolitis), skin symptoms (hand- foot- and mouth disease exanthema), G-I symptoms (stomatitis, herpangina, vomiting, diarrhoea)	Virussepsis, meningoencephalitis, perimyocarditis, hepatitis, coagulopathy, myositis, pneumonia
Metapneumovirus	Rhinorrhea, congestion, cough, bronchiolitis, fever, apnoeas, acute respiratory failure	Pneumonia, AOM
Parechovirus	Nonspecific febrile illness – sepsis-like disease, mild respiratory or G-I symptoms	Meningoencephalitis, virussepsis, AOM
Influenza A, B	Respiratory distress, temperature instability, sepsis-like disease	AOM, pneumonia, laryngitis, CNS manifestations, myocarditis, myositis
Parainfluenza 1–4	Rhinorrhea, congestion, cough, bronchiolitis, fever	Pneumonia
Respiratory syncytial virus	Rhinorrhea, congestion, cough, bronchiolitis, fever, apnoeas, acute respiratory failure	Pneumonia, AOM, rarely: meningoencephalitis, perimyocarditis, hepatitis
Rhinovirus	Rhinorrhea, congestion, cough, irritability, fever, sepsis-like disease	Pneumonia, AOM
Virus	**Prognosis**	**Long-term sequelae**
Adenovirus	Usually good. Mortality is high in neonates with pneumonia (50%) and disseminated disease (75%)	No data available
Bocavirus-1	Good	Adverse neurological sequelae have been reported after encephalitis
Coronavirus	Usually good	No data available
Enteroviruses	Usually good, but can be fatal. Virussepsis caused by coxsackievirus B or echovirus has a high mortality (50%)	May act as an environmental trigger for type 1 -diabetes. Persistent hepatic and cardiac dysfunction and neurodevelopmental deficits have been reported after severe enterovirus disease
Metapneumovirus	Usually good	No data available
Parechovirus	Usually good	Parechovirus-3 encephalitis is shown to be associated with CNS white matter changes and with adverse neurodevelopmental long-term sequelae
Influenza A, B	Usually good. Can be fatal	No known long-term sequelae
Parainfluenza 1–4	Usually good	No data available
Respiratory syncytial virus	Usually good. Can be fatal	Recurrent wheeze, asthma, asthma, allergic sensitisation
Rhinovirus	Usually good. Can be fatal	Recurrent wheeze, asthma

AOM = Acute otitis media; CNS = Central nervous system; CLD = Chronic lung disease; CHD = Congenital heart disease; CF = Cystic fibrosis; G-I = Gastrointestinal.
*Clinically significant congenital heart disease.

or decreased body size when they are infected and pre-existing medical conditions affecting lung function (14). Other factors affecting the severity of neonatal respiratory virus infections include the type of virus, the virus serotype/genotype, mode of transmission and the presence of passively acquired, specific maternal antibodies. Significant correlations between the genes in the immune system and the risk of severe respiratory virus infection have been observed. For example, in preterm infants single-nucleotide polymorphisms in several genes have been shown to be associated with the risk of developing severe RSV infections independent of premorbid lung function (25). Furthermore, decreased innate immune cytokine responses have been shown to correlate with disease severity not only in RSV but also in rhinovirus bronchiolitis (26). Multiple respiratory virus detection occurs in 20–40% of children with respiratory virus infections, but this finding seems to be less common in young infants. In many studies, the bocavirus-1 plus a rhinovirus has been the most common combination of multiple viruses. Whether coinfections contribute to disease severity is currently unclear (27). Likewise, the clinical significance of viral load on the disease severity has not yet been established.

DIAGNOSTICS

With the exception of influenza, knowledge of the infecting viral agent does not usually alter the treatment due to the fact that clinically useful antiviral agents do not exist for most respiratory viruses. The virological diagnosis of infants treated as outpatients is not always necessary as it does not predict the severity or length of the disease. It may, however, guide the decision about whether the infant should be hospitalised or treated as an outpatient. The detection of the viral aetiologic agent in hospitalised infants is important with regard to understanding the clinical manifestations, for guiding the cohorting of patients and for the prevention of nosocomial infections. In addition, virological diagnosis provides essential data for the development of prevention strategies (14).

Previously, viral diagnostics was based on virus culture, serology or antigen detection. These labour-intensive and slow diagnostic methods have nowadays been replaced with PCR tests. With the rapid development of high-throughput molecular techniques, several new viruses associated with respiratory diseases, such as the bocavirus-1, metapneumovirus and coronavirus have been identified, and our knowledge of respiratory virus infections has substantially increased. PCR tests are also significantly more sensitive than the other methods, which has increased the rates of viral detection. Over the past decade, PCR tests have been multiplexed and it is now possible to screen up to 16–20 respiratory viruses concurrently from a single mucus sample with a flocked nasal swab (28). However, it must be kept in mind that the sensitivity of multiplex PCR tests is not as high as that of PCR tests for detecting a single virus. It should also be emphasised that in contrast to a positive virus culture, a positive PCR test does not necessarily reflect active virus replication. A rhinovirus PCR test is positive during and after symptomatic infection, in subclinical infection, or just in an innocent contamination (15). Transcriptional profiling is a useful tool for discriminating between an active infection and incidental virus detection (29). With respect to the impact of the viral load, the available studies have provided conflicting results about the correlation between viral load and either infectiousness or the presence of infectious viral particles (15).

One important issue to be considered is the role of respiratory viruses in the differential diagnosis of neonatal early-onset (<72 hours) sepsis and especially of late-onset (>72 hours) sepsis, as well as of nosocomial sepsis involving inborn infants who have not yet been discharged home. Most respiratory viruses are acquired postnatally through close contact with infected caregivers. Nevertheless, current evidence supports the concept that the transmission of some viruses to neonates may also occur during the antenatal period through maternal viraemia and transplacental spread to the foetus, or perinatally by exposure to maternal infected secretions (30). The onset of symptoms following infection with respiratory viruses varies from 24 hours to several days. As described earlier, the initial signs and symptoms of respiratory virus diseases in neonates can be identical to those seen in bacterial infections. Furthermore, routine laboratory markers are inconclusive in differentiating bacterial from viral infections, especially during the early phase of the disease. In a recent study in children aged from one to 24 months, interferon inducible myxovirus resistance protein A had a 92% sensitivity for symptomatic respiratory virus infections (31). Because the outcome of a neonatal bacterial infection is markedly improved if the illness is recognised early and appropriate antimicrobial agents are administered promptly, it is plausible that viral diseases in neonates are often treated with broad-spectrum antibiotics (11). Thus, we recommend that any infant with suspected late-onset or nosocomial sepsis or signs of a serious infection, should also be evaluated for the most common respiratory viruses with multiplex PCR test from nasopharyngeal specimens, in addition to a complete sepsis workup (10,13). Practitioners could also be advised to order a multiplex PCR test for respiratory viruses in infants if they demonstrate an early-onset sepsis-like clinical presentation and bacterial samples remain negative. Because preterm infants, in particular, may not have classic cold symptoms during respiratory tract infections, routine detection of respiratory viruses should also be proposed if neonates treated in NICUs present with respiratory symptoms or clinical deterioration.

To avoid unnecessary long courses of antibiotics, discontinuing medication could be considered in cases where a respiratory virus is detected. New and more sensitive biomarkers for bacterial infections are much needed. The possibility of concomitant bacterial co-infection must, however, always be kept in mind. Bacterial involvement in a virus-associated lower respiratory tract infection is possible. Furthermore, serious bacterial complications, such as a pulmonary abscess, have been reported to be associated

with an RSV infection in a neonate (32). Respiratory virus infections are also often associated with bacterial complications such as acute otitis media and pneumonia that require antibiotic treatment.

TREATMENT

At present, there are no approved specific antiviral treatments for respiratory viruses other than influenza viruses. In the absence of antivirals, the mainstays of treatments for severe virus disease are supportive care, including oxygen and mechanical ventilation if needed, cardiorespiratory support and appropriate fluid replacement. Analgesics and antipyretics and, in some cases, nasal decongestants, such as oxymetazoline hydrochloride, may be helpful in reducing discomfort and symptoms, making feeding easier and allowing for an adequate supply of oral fluids (14).

For influenza A and B viruses, the neuraminidase inhibitor oseltamivir is licensed for use in young children. Due to the fact that influenza can be potentially fatal in children with and without high-risk medical conditions, it has been recommended that antiviral treatment should be given as early as possible to children who are hospitalised, who have a severe, complicated or progressive illness or who are at high risk of complications, because they are under the age of two or have an underlying medical conditions (19,33). Prompt treatment with neuraminidase inhibitor in the first 36 hours after symptoms has been shown to improve survival, decrease the need for mechanical ventilation, shorten the illness duration and also shorten viral shedding (33).

Many antiviral drugs against RSV are currently being developed, but none of them are commercially available yet (34). With regard to other respiratory viruses, ribavirin shows *in vitro* inhibitory activity against the RSV, parainfluenza viruses, metapneumovirus and group C adenovirus, but ribavirin treatment may have significant adverse effects for both the patient and health-care workers and its clinical efficacy is questionable. Severe adenovirus diseases have been treated with cidofovir, with or without intravenous immune globulin, but with poor efficacy (18). Immune globulin may be also beneficial in life-threatening enterovirus and parechovirus infections in neonates, but proof of its efficacy is still lacking (35). The antiviral drug pleconaril has been shown to be efficient and safe for the treatment of neonates with enterovirus sepsis (36).

PREVENTION

Enhanced virus surveillance and optimised infection control should be implemented in all NICUs to avoid transmitting viruses and to limit the spread of infection. It is advisable to have a separate neonatal unit that does not accept admissions from home. In the future, modern hospital architecture, with single family rooms in NICUs, could substantially reduce the rate at which infants acquire infectious organisms during their hospital stay. Restricting visitors to neonatal units during virus outbreaks in the community could also be a reasonable precaution. Symptomatic parents may transmit viruses to their infant. The risk of virus infection should be weighed against the disadvantages of parent-infant separation if excluding the symptomatic parents from the hospital is the customary practice. Virus-positive infants should be strictly isolated and cared for by nurses who are not responsible for caring for infants without the virus. It is also advisable to monitor the duration of virus shedding, which may last several weeks, and continue isolation measures until all infants in the room have been documented as being virus-negative. Strict hygiene measures, in particular, hand washing with soap and water, have been shown to reduce respiratory viral transmission and thus to diminish the incidence of viral respiratory tract infections (37). However, due to the complicated transmission of respiratory viruses, preventive measures only provide partial control of virus transmission.

Currently, the only available vaccine for respiratory viruses is against the influenza A and B viruses. Because influenza vaccines are not licensed for children under six months old, the optimal evidence-based strategy to protect infants is to administer the inactivated influenza vaccine to pregnant women (17). It is now well established that influenza vaccination during pregnancy is safe and reduces the risk of disease in both women and their infants (38). It has been suggested that the protection mechanism in infants is the acquisition of hemagglutinin antibodies, either through the placenta of breast-feeding, or indirectly by preventing influenza infections in the mothers. Oseltamivir can also be used for postexposure prophylaxis of influenza in at-risk infants if it can be given within 48 hours after exposure (7). To protect infants treated in NICUs, annual vaccinations of all healthcare workers against seasonal influenza are strongly recommended (39). Unfortunately, compliance with vaccination recommendations is generally low and exposure to infected staff as the source of nosocomial outbreaks is possible.

Despite long-term efforts to develop safe and efficacious vaccines against RSV, no existing licensed vaccines or soon to be released vaccines are available for the disease (34). Studies of RSV vaccination in pregnancy are in progress, making maternal vaccination a potentially realistic intervention for protecting infants against RSV disease in the near future. The monoclonal antibody, palivizumab, was demonstrated to decrease RSV-related hospitalisations in one cohort by 50% (40). Palivizumab has also been shown to significantly decrease subsequent wheezing days during the first years of life (41,42). Interestingly, the effect of prevention on the number of wheezing days has been shown to persist to the post-prophylaxis period. Palivizumab is administered intramuscularly once a month throughout the RSV season, normally in four to five doses. Promising results have also been published on how the early administration of palivizumab terminated an RSV epidemic in a NICU (43). Attempts to develop vaccines against rhinoviruses have failed because of the large number of viral types and the lack of cross-serotype protection generated (44).

Modulating gut microbiota to prevent bacterial and viral respiratory tract infections in infants has been of great interest over the past decade, although the antiviral mechanisms of probiotics are unclear. In one study, a significant reduction in the incidence of respiratory tract infections, and especially of rhinovirus infections, was achieved during the first year of life in a preterm population who received prebiotic and probiotic supplementation during the first two months of life (45).

LONG-TERM CONSEQUENCES OF RESPIRATORY VIRUS INFECTIONS

To date, early-life respiratory virus infections and their long-term consequences have largely remained an uncharted territory, mainly because of slow and unreliable diagnostic methods and the lack of long-term follow-up data. However, it has been increasingly recognised that a respiratory virus infection during the first year of life may have an impact on later health, especially on pulmonary outcomes. It has been suggested that the magnitude of subsequent health-related effects is more profound if the infection occurs early in life, during a critical window, when the infant's immune system is still immature. Although the acute infection will be resolved and the virus cleared, an immunologic scar may develop and persist and result in a long-lasting immune dysfunction (46).

Abnormal lung function development in prematurely born infants appears to be an important contributor to their vulnerability to viral respiratory tract infections. Furthermore, acquiring these infections during the neonatal period has been shown to affect adversely infants′ lung function (47). Having a rhinovirus infection in infancy has been shown to be associated not only with chronic respiratory morbidity in preterm infants without previous lung pathology (48) but also with increased healthcare use and health-related care costs during infancy (49). In addition, RSV infections during the first year of life have also been shown to be associated with increased healthcare use and care costs, which continued during the second year of life (50).

Respiratory virus infections may have long-term consequences for both premature and term-born infants. In a healthy term-born population, a lower respiratory tract infection in the first year of life has been shown to be associated with a worse lung function in adult life (51). Numerous investigations into the development of asthma have revealed that bronchiolitis has been associated with recurrent wheezing and asthma in later childhood (52). It was previously thought that, in particular, RSV-associated wheezing predisposed infants to subsequent recurrent wheeze and asthma development, particularly preterm infants. There is now solid evidence that rhinovirus-induced wheezing in infancy is an even stronger predictor of subsequent wheezing and the development of asthma, followed by a positive family history for asthma or atopy (53).

It remains to be clarified whether the respiratory virus infection is the actual cause of recurrent wheezing or merely the first indication of pre-existing pulmonary vulnerability (2). There is evidence to suggest that both genetic and environmental factors contribute to the host immune response to early-life respiratory virus infections and that this response, in turn, may adversely affect the development of lungs and the control mechanisms of the lower airways. Furthermore, certain single-nucleotide genetic polymorphisms have been shown to be associated with chronic respiratory morbidity and asthma following RSV infection (54). Although it is conceivable that respiratory viral infections might lead to the development of asthma, by damaging the developing airways or altering the immune response (55), it has also been suggested that viral infections may simply reveal a pre-existing tendency for asthma by inducing mucous metaplasia and airway hyperresponsiveness (56). Nevertheless, it is probable that there are multiple known and also unknown risk factors that contribute to the overall inception of asthma, acting independently or in conjunction.

Growing evidence suggests that respiratory virus infections during the first months of life may also have other adverse long-term consequences than pulmonary outcomes. Enteroviruses are among the suspected environmental triggers in the induction of type 1 diabetes, a disease in which T cell-mediated autoimmune processes target insulin-producing beta cells in the pancreas. Enteroviruses, and in particular the group B coxsackievirus, appear to have the ability to damage beta cells (57), although the conclusive causative relationship between an enterovirus infection and the development of type 1 diabetes remains to be established (58). Early-life enterovirus infections may also be associated with persistent hepatic and cardiac dysfunction and neurodevelopmental deficits among survivors (19). Parechovirus infections during the neonatal period have been shown to be associated with central nervous system white matter changes and delayed neurological development (59,60). Therefore, longitudinal follow-up and routine cognitive evaluation are necessary to document the long-term consequences of the human parechovirus infection in infancy.

CONCLUSION

Respiratory viral infections are not uncommon among neonates treated in NICUs. Given the significant burden of respiratory virus infections among this highly susceptible population, and the limited prevention tools that are available, a focus on appreciating and containing the consequences of these infections is warranted. It can be recommended that any infant with signs of infection should also be suspected of having a respiratory virus infection. Simple flocked nasal swabs and multiplex PCR tests are recommended as diagnostic methods. Furthermore, all available preventive and curative modalities against viral respiratory tract infections during the neonatal period should be implemented. Preventing nosocomial virus infections by using intensified hygiene measures and cohorting infected infants should be a major goal in NICUs. Further research, active virus surveillance and long-term follow-up

are also needed to ascertain the causality and the exact underlying mechanisms for adverse long-term consequences.

CONFLICT OF INTEREST

None.

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